32, lines 26-30. Claims 16-19 were amended to correct antecedent basis. Support for new claim 37 can be found, for example, in original claim 15 and on page 8, lines 29-31; page 11, lines 6-13; page 13, line 32, to page 14, line 2; page 15, lines 1-13; page 31, lines 23-33; and page 32, lines 26-30. Support for new claims 38-41 can be found, for example, in original claims 16-19. Accordingly, these amendments and new claims do not raise an issue of new matter and entry thereof is respectfully requested.

Applicant has set forth the amendment to the claims in clean form above and in Appendix A, with marked up amendments indicated with brackets and underlining.

Rejections Under 35 U.S.C. § 112

The rejection of claims 15-19 under 35 U.S.C. § 112, first paragraph, as allegedly lacking sufficient description to convey to one skilled in the art that Applicant was in possession of the claimed invention at the time the application was filed is respectfully traversed. Applicant submits that the specification provides sufficient description and guidance to convey that Applicant was in possession of the claimed methods at the time the application was filed.

Claim 15, as amended, is directed to a method for identifying a bi-target ligand to enzymes in an enzyme family. The method includes the steps of (a) identifying a first bi-ligand to a first enzyme in the enzyme family, wherein the bi-ligand comprises a common ligand, wherein the common ligand

competes for cofactor binding to an enzyme in the enzyme family, and a first specificity ligand, wherein the specificity ligand binds to a substrate binding site of the first enzyme; (b) identifying a second bi-ligand to a second enzyme in the enzyme family, wherein the bi-ligand comprises the common ligand and a second specificity ligand, wherein the specificity ligand binds to a substrate binding site of the second enzyme; and (c) generating a bi-target ligand comprising the common ligand, the first specificity ligand and the second specificity ligand, whereby the bi-target ligand can bind to the first enzyme and the second enzyme.

The Office Action refers to various terms recited in the claims, in particular, "common ligand," "conserved site," "specificity ligand," "specificity site," "receptor family," and "expansion linker" and indicates that the definition of these terms is broad. Applicant points out that the terms "conserved site" and "expansion linker" have been deleted from the claims.

Regarding the term "receptor family," Applicant points out that this term has been amended to "enzyme family." With respect to an enzyme family, the specification teaches that a receptor family is a group of two or more receptors that share a common, recognizable amino acid motif that is conserved between members of the receptor family and can be enzymatic activity of an enzyme family (page 10, line 32, to page 13, line 23). The specification also teaches numerous exemplary enzyme families (page 11, line 6, to page 13, line 6). The specification further teaches methods for determining that enzymes are in the same

family, including the ability to bind a cofactor (page 11, line 14, to page 13, line 6; and page 19, line 25, to page 25, line 17). Accordingly, one skilled in the art would readily understand the meaning of an enzyme family and could readily determine whether two enzymes are in the same enzyme family based on the teachings in the specification.

With regard to the term "common ligand," claim 15 has been amended to recite that the common ligand competes for cofactor binding to an enzyme in an enzyme family. The specification teaches that a common ligand binds to a conserved site in a receptor, that a receptor can be an enzyme, that a conserved site of an enzyme is a cofactor binding site, and that a common ligand that binds to a conserved site competes for cofactor (natural common ligand) binding (page 8, line 29, to page 9, line 3; page 11, lines 6-13; page 13, line 32, to page 14, line 2; page 31, lines 23-33; and page 32, lines 26-30). Furthermore, the specification teaches methods for identifying common ligands by competing for a natural common ligand (page 30, line 29, to page 33, line 12). Thus, based on the teachings in the specification, one skilled in the art would readily understand the meaning of a common ligand and how to identify such a common ligand that competes for cofactor binding.

With regard to the term "specificity ligand," claim 15 has been amended to recite that the specificity ligand binds to a substrate binding site of an enzyme in the enzyme family. The specification teaches that a specificity site of an enzyme is a substrate binding site that distinguishes two members of a family

that exhibit substrate specificity (page 15, lines 1-13). Therefore, one skilled in the art would readily know the meaning of a specificity ligand that binds to a substrate binding site of an enzyme in the enzyme family based on the teachings in the specification.

Furthermore, the specification provides examples of how to make and use the invention, as claimed. The specification teaches that a bi-ligand is identified by determining a common ligand that binds to at least two target receptors in a receptor family (page 29, lines 7-9). The specification also teaches methods of identifying a common ligand, for example, by selecting candidate compounds based on structural similarities, screening of commercially available compounds, or using structural information and commercially available databases to identify common ligands (page 31, line 23, to page 32, line 25). The specification additionally teaches that a common ligand can be identified by screening for competitive binding to a natural common ligand (page 30, line 29, to page 31, line 22; and page 32, lines 26-30).

The specification further teaches that methods such as NMR can be applied to identify sites on a common ligand proximal to a specificity site (page 34, line 5, to page 39, line 17). The specification also teaches that a linker is attached to the common ligand so that the linker is oriented towards the specificity site (page 39, line 18, to page 43, line 6) and that a bi-ligand is generated by attaching potential specificity ligands having reactive groups to the linker at the position on

the linker that orients the specificity ligand to the specificity site (page 43, lines 19-27). The specification additionally teaches that a population of bi-ligands can be used to identify ligands for a receptor in a receptor family and therapuetic agents (page 16, line 16, to page 19, line 13). Moreover, the specification teaches that two specificity ligands can be combined with a common ligand to generate a bi-target ligand (page 7, line 28, to page 8, line 3; and page 47, line 16, to page 48, line 16). Accordingly, the specification teaches the claimed method of identifying a bi-target ligand to enzymes in an enzyme family. Therefore, Applicant submits that the specification provides sufficient description and guidance to convey to one skilled in the art that Applicant was in possession of the claimed invention at the time the application was filed. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

The rejection of claims 15-19 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement is respectfully traversed. Applicant submits that the specification provides sufficient description and guidance to enable the claimed methods.

Regarding the assertion in the Office Action about the breadth of the claims, the Office Action indicates that the "common ligand" and "specificity ligand" must bind their respective sites and the sites must be able to be determined. Claim 15, as amended, recites that the common ligand competes for cofactor binding to an enzyme in the enzyme family. The claim

also recites that the specificity ligand binds to a substrate binding site of an enzyme. Thus, the claims clearly recite the characteristics of the common ligand and specificity ligand, and one skilled in the art would readily be able to determine these characteristics based on the teachings in the specification and methods well known to those skilled in the art.

Applicant respectfully disagrees with the assertion in the Office Action regarding the level of predictability of the art that only limited numbers of compounds that interact with enzyme targets were known in the art at the time of filing. Numerous examples of compounds that bind to cofactor or substrate binding sites were well known to those skilled in the art at the time the application was filed. Moreover, one skilled in the art would have readily been able to determine a common ligand that competes for binding to an enzyme by using well known screening methods and as taught in the specification (see page 30, line 29, to page 33, line 12). Similarly, one skilled in the art would have readily been able to determine a specificity ligand that binds to a substrate binding site of an enzyme using well known methods. Accordingly, Applicant respectfully submits that one skilled in the art would have readily been able to identify a bi-target ligand as in the claimed methods.

With regard to the lack of working examples, Applicant respectfully points out that working examples are not required. Furthermore, the specification provides examples of how to make and use the invention, as claimed. As discussed above, the specification teaches that a bi-ligand is identified by

determining a common ligand that binds to at least two target receptors in a receptor family (page 29, lines 7-9). The specification also teaches methods of identifying a common ligand, for example, by selecting candidate compounds based on structural similarities, screening of commercially available compounds, or using structural information and commercially available databases to identify common ligands (page 31, line 23, to page 32, line 25). The specification additionally teaches that a common ligand can be identified by screening for competitive binding to a natural common ligand (page 30, line 29, to page 31, line 22; and page 32, lines 26-30).

The specification further teaches that methods such as NMR can be applied to identify sites on a common ligand proximal to a specificity site (page 34, line 5, to page 39, line 17). The specification also teaches that a linker is attached to the common ligand so that the linker is oriented towards the specificity site (page 39, line 18, to page 43, line 6) and that a bi-ligand is generated by attaching potential specificity ligands having reactive groups to the linker at the position on the linker that orients the specificity ligand to the specificity site (page 43, lines 19-27). The specification additionally teaches that a population of bi-ligands can be used to identify ligands for a receptor in a receptor family and therapuetic agents (page 16, line 16, to page 19, line 13). Moreover, the specification teaches that two specificity ligands can be combined with a common ligand to generate a bi-target ligand (page 7, line 28, to page 8, line 3; and page 47, line 16, to page 48, line 16). Accordingly, Applicant submits that the

specification provides examples of how to make and use a bi-target ligand using the claimed methods. Therefore, Applicant submits that the specification provides sufficient description and guidance to enable one skilled in the art to make and use the invention as claimed.

In view of the teachings in the specification and methods well known to those skilled in the art, Applicant submits that the specification provides sufficient description and guidance to enable the claimed methods of identifying a bi-target ligand. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

CONCLUSION

In light of the amendments and remarks herein, Applicant submits that the claims are now in condition for allowance and respectfully requests a notice to this effect. The Examiner is invited to call the undersigned agent or Cathryn Campbell if there are any questions.

Respectfully submitted,

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APPENDIX A

Please amend the claims as follows:

15. (Amended) A method for identifying a bi-target ligand to **[a receptor]** **enzymes in an enzyme family**, comprising

(a) identifying a first bi-ligand to a first **[receptor]** **enzyme** in **[a receptor]** **said enzyme** family, wherein said bi-ligand comprises a common ligand**, wherein said common ligand competes for cofactor binding to an enzyme** **[to a conserved site]** in **[a receptor]** **said enzyme** family, and a first specificity ligand**, wherein said specificity ligand binds to a substrate binding site of** **[to]** said first **[receptor]** **enzyme**;

(b) identifying a second bi-ligand to a second **[receptor]** **enzyme** in said **[receptor]** **enzyme** family, wherein said bi-ligand comprises said common ligand and a second specificity ligand**, wherein said specificity ligand binds to a substrate binding site of** **[to]** said second **[receptor]** **enzyme**; and

(c) generating a bi-target ligand comprising said common ligand, said first specificity ligand and said second specificity ligand, whereby said bi-target ligand can bind to said first **[receptor]** **enzyme** and said second **[receptor]** **enzyme**.

16. (Amended) The method of claim 15, wherein said **[receptor is an]** enzyme **family is** selected from the group consisting of kinases, dehydrogenases, oxidoreductases, GTPases, carboxyl transferases, acyl transferases, decarboxylases, transaminases, racemases, methyl transferases, formyl transferases, and α-ketodecarboxylases.

17. (Amended) The method of claim 15, wherein said **[receptor]** **enzyme** family binds a cofactor selected from the group consisting of nicotinamide adenine dinucleotide, nicotinamide adenine dinucleotide phosphate, thiamine pyrophosphate, flavin adenine dinucleotide, flavin mononucleotide, pyridoxal phosphate, coenzyme A, tetrahydrofolate, adenosine triphosphate, guanosine triphosphate and S-adenosyl methionine.

18. (Amended) The method of claim 15, wherein said **common ligand and said specificity ligands are attached by a** **[expansion]** linker **[has]** **having** approximate C2 symmetry.

19. The method of claim 18, wherein said **[expansion]** linker has perfect C2 symmetry.